

# *Chlamydia trachomatis* and oral contraceptive use: a quantitative review

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## Abstract

**Objectives**—*Chlamydia trachomatis* is now recognised as a major sexually transmitted disease; oral contraceptive use is rapidly increasing particularly in developing countries. There are thus important public health implications of the many reports that isolation of *C trachomatis* is more frequent among users of oral contraceptives. The aim of this analysis was to assess the strength and consistency of this association by summarising published studies between 1972 and 1990.

**Design**—Studies identified were grouped according to whether they were prospective or case-control studies. Data were extracted and pooled estimates of the unadjusted odds ratios were made for all studies, as well as for sub-groups defined by an index of study quality, background prevalence of *C trachomatis*, and the contraceptive comparison being made.

**Location**—Studies in the analysis were mainly conducted in Europe and North America; the meta-analysis was done at the Harvard School of Public Health, Boston, MA, USA.

**Results**—The pooled estimated unadjusted odds ratio for 29 case-control studies examined was 1.93 (95% CI, 1.77–2.11), indicating an almost twofold increased risk of chlamydial infection for oral contraceptive users. Neither study quality nor prevalence of *C trachomatis* modified this risk. When compared to the use of barrier contraceptives, however, the risk of infection for women using oral contraceptives increased to 2.91 (95% CI, 1.86–4.55). The pooled estimated protective effect of barrier methods in these studies was 0.34 (95% CI, 0.22–0.54).

**Conclusions**—Cross-study comparisons of the relationship between oral contraceptive use and chlamydial infection are limited by the design and analysis of many component studies which did not control for confounding factors such as sexual behaviour and age. The almost twofold risk of increased chlamydial infection for oral contraceptive users, supported by the findings of two prospective studies, however, points to the importance of considering the risks and benefits of oral contraceptive use in women who are likely to be exposed to *C trachomatis* and other STDs. The protective effect of barrier methods emphasizes the continued need

for promoting barrier methods of contraception.

## Introduction

*Chlamydia trachomatis* has emerged as a major sexually transmitted disease organism over the past decade and a half. In North America and Western Europe prevalence of this infection is between 4.9% and 35% in women, and between 3% and 20% in men, depending on the population (see table 1), and in the United States it has been estimated that the annual incidence of chlamydial infections is around 4 million,<sup>1</sup> surpassing gonorrhoea as the most common sexually transmitted disease. A picture of worldwide prevalence of *C trachomatis* or any other reproductive tract infection is not available at the present time, but the sparse existing data document a *C trachomatis* prevalence in women of between 6% and 28% in Africa<sup>2,3,4,5,6</sup> and 2% to 63% in some Asian countries.<sup>3,7</sup>

At the same time, use of the oral contraceptive pill as a method of contraception has increased dramatically, especially in developing countries. Of the estimated 65 million women worldwide who use oral contraceptives, 40 million are in developing countries where the number of women using this method has nearly trebled from 14 million in 1977. In developed countries, the number of women using oral contraceptives has stabilised at around 25 million since the end of the 1970s, but as a proportion of overall contraceptive use, the method has declined in many of these countries.<sup>8</sup>

A number of studies carried out in the past 15 years have implicated oral contraceptives as a co-factor for chlamydial infection. Current knowledge on AIDS also suggests that other sexually transmitted diseases (STDs) may contribute to the spread of HIV infection.<sup>9</sup> Thus the relation between oral contraceptives and chlamydial and other sexually transmitted infections is an important public health issue.

*C trachomatis* is a pathogen of the squamocolumnar cells that are found within the transitional zone of the cervix.<sup>10</sup> Because oral contraceptives can induce ectopy (a condition where the transitional zone of the cervix is moved from the endocervical canal to the ectocervix) it is possible that women taking oral contraceptives are more prone to chlamydial infection because more susceptible cells are exposed to infection. Alternatively, an observed association between oral contraceptive use and chlamydial infection might reflect

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Table 1 Association of chlamydia with oral contraceptive use, published case-control studies

Date	Study (Ref. No.)	Sample size	Sample setting	Chlamydia Prevalence	Crude odds ratio	Confidence intervals
1974	Hilton <i>et al.</i> <sup>14</sup> Bristol, U.K.	279	STD clinic	31.0%	2.54	1.44-4.47
1975	Burns <i>et al.</i> <sup>15</sup> London, U.K.	638	STD clinic	11.9%	1.18	0.71-1.96
1977	Woolfitt & Watt <sup>42</sup> Manchester, U.K.	154	STD clinic	26.0%	0.98	0.44-2.16
1978	Oriel <i>et al.</i> <sup>16</sup> London, U.K.	259	STD clinic	21.6%	2.06	1.08-3.94
1978	Ripa <i>et al.</i> <sup>37</sup> Lund, Sweden	78	Ob/gyn Outpatient dept.	19.3%	4.02	1.17-14.51
1980	Tait <i>et al.</i> <sup>13</sup> Liverpool, U.K.	202	STD clinic	34.7%	2.86	1.5-5.5
1981	Arya <i>et al.</i> <sup>43</sup> Liverpool, U.K.	208	STD clinic	33.3%	3.36	1.54-7.47
1981	Kinghorn & Waugh <sup>17</sup> Leeds, U.K.	1080	STD clinic	21.1%	2.05	1.49-2.82
1981	Svensson <i>et al.</i> <sup>41</sup> Lund, Sweden	427	Gyn. outpatient	9.2%	2.63	1.67-4.15
1983	Fraser <i>et al.</i> <sup>18</sup> Oklahoma Cty, USA	123	Adolescent clinic	8.0%	4.55	1.03-21.04
1983	Schachter <i>et al.</i> <sup>10</sup> San Francisco, USA	1907	5 family planning clinics, 2 teen clinics	9.8%	2.69	1.85-3.93
1984	Chacko & Lovchik <sup>33</sup> Baltimore, USA	174	Adolescent clinics	23.0%	1.30	0.62-2.71
1984	Shafer <i>et al.</i> <sup>12</sup> San Francisco, USA	301	Teen family clinic	15.3%	2.52	1.34-4.74
1985	Harrison <i>et al.</i> <sup>21</sup> Atlanta, USA	161	Student health service	8.0%	3.33	0.92-12.5
1985	McCormack <sup>19</sup> Boston, USA	381	Student health service	5.8%	3.91	1.25-16.17
1986	Handsfeld <i>et al.</i> <sup>45</sup> Seattle, USA	1034	Family planning clinics (2)	9.3%	1.78	1.12-2.82
1986	Jaffe <i>et al.</i> <sup>32</sup> New York, USA	95	Adolescent clinics	26.3%	2.11	0.75-6.03
1987	Addiss <i>et al.</i> <sup>44</sup> Wisconsin, USA	335	Family planning clinics (4)	10.7%	1.50	0.68-3.39
1987	Lefèvre <i>et al.</i> <sup>22</sup> Toulouse, France	370	University clinic	7.7%	3.48	1.49-8.28
1988	Blum <i>et al.</i> <sup>38</sup> Givataym, Israel	158	Family planning clinic	26.6%	2.55	1.16-5.60
1988	Evans <i>et al.</i> <sup>27</sup> Oklahoma, USA	152	Adolescent clinic	13.0%	1.16	0.4-3.36
1988	Magder <i>et al.</i> <sup>36</sup> Denver, USA	1014	STD clinic	17.0%	1.51	1.04-2.20
1988	Ruijs <i>et al.</i> <sup>26</sup> Groningen, Netherlands	197	University hospital family planning clinic	5.5%	6.04	1.37-36.23
1989	Oh <i>et al.</i> <sup>29</sup> Birmingham, USA	367	Teen clinic	19.4%	1.51	0.85-2.69
1990	Barnes <i>et al.</i> <sup>35</sup> Indianapolis, USA	5276	STD clinic	24.6%	1.75	1.53-1.99
1990	Bro & Juul <sup>40</sup> Aarhus, Denmark	577	General practice	6.8%	2.87	1.4-5.8
1990	MacCaulay <i>et al.</i> <sup>25</sup> Manchester, U.K.	452	Family planning clinic	7.3%	3.76	1.66-8.71
1990	Pereira <i>et al.</i> <sup>39</sup> Halifax, Canada	244	STD clinic	27.4%	2.08	1.13-3.87
1990	Winter <i>et al.</i> <sup>30</sup> Camp Hill, USA	860	Family planning clinics	11.2%	1.87	1.15-3.04

enhanced detection of *C trachomatis* through more efficient sampling from the cervix.

A number of studies have reported on the relation between oral contraceptives and *C trachomatis*, but many of these have been small, with wide confidence intervals. A previous review<sup>11</sup> compares some study results but does not quantify them. To overcome this difficulty, we performed a meta-analysis of 29 case-control studies in which the relationship between oral contraceptive use and *C trachomatis* was measured. Several methodological problems inherent in the studies are discussed, and pooled odds ratios are presented. Two prospective studies are also discussed, and we make recommendations for research and practice.

## Methods

Studies for inclusion in the meta-analysis were

identified through a MEDLINE search of literature from 1972 through 1990, and through scanning of the references cited in the articles recovered from this search. No unpublished studies were sought out. Thirty-five studies were identified,<sup>10 12-45</sup> of which four<sup>20 23 28 34</sup> were excluded from the analysis because of inadequate reported data. Of the 31 remaining studies, 29 were case-control studies (or cross-sectional studies which can be analyzed in a case-control manner) (table 1), and two were prospective studies<sup>24 31</sup> (table 2).

## Quality assessment

The quality of a study may affect the validity of the results. For this reason, it is pertinent in meta-analysis to explore the relation between study quality and study outcome. We identified five major areas contributing to higher quality studies, and constructed a quality index which rated studies from a low of 0 to a high of 14.

Table 2 Association of *C. trachomatis* with oral contraceptive use: prospective studies

Study	Sample size	Sample Setting	Chlamydia OC use relative risk	Confidence intervals	Exposure	Comments
Louv <i>et al.</i> 1989 Birmingham, USA <sup>24</sup>	818	STD Clinic	1.95 1.73	1.1-2.8 ( <i>p</i> = 0.022)	OC vs IUD or steriliz.	Crude estimate  Adjusted for no. of partners/sex activity age and gravidity
Avonts <i>et al.</i> 1989 Ghent, Belgium <sup>31</sup>	231	Family practice	8.8 1.7 6.0	1.3-59.0 0.2-7.0 2.0-14.0	OC vs IUD  one partner 2 partners +	

(Index points were awarded on the basis of whether studies had the following: prior hypothesis of an association 1, none 0; definition of oral contraceptive exposure: one point in time 0, one month continuous use prior to study 1, more than one month continuous use prior to study 2; definition of non-exposure: non-oral contraceptive use 0, other contraceptive methods/no contraception 1, use of barrier methods 2; exclusion criteria: none 0, pregnancy 1, recent use of antibiotics 1; confounding: no controlling for confounding 0, one additional point for controlling each of: number of sex partners, age, a history of STDs, socio-economic status and/or race, gravidity, and cervical ectopy, for a total of 7. (See description of methodological problems.)) We then examined pooled odds ratios to see if the observed association was modified by study quality.

#### Methodological problems

These five areas also constituted major sources of variability among the studies, which present problems for conducting a meta-analysis.

(1) *Prior hypothesis.* If studies are specifically designed to examine the relationship between oral contraceptive use and *C. trachomatis*, they may be more likely to be designed in such a way as to examine that relationship carefully, possibly providing a more valid test of the hypothesis. Only five of the studies listed here set out specifically to examine the relationship between *C. trachomatis* and oral contraceptive use. Most (nineteen) of the studies' objectives were to determine the risk factors for *C. trachomatis* so that screening could be targeted, because such a high percentage of women infected are asymptomatic, and laboratory diagnostic methods are expensive.

(2) *Definition of exposure.* A problem with case-control studies in which exposure and disease status are assessed at a single point in time, is that we cannot be sure which occurred first. An asymptomatic woman infected with *C. trachomatis* and currently using oral contraceptives may have begun oral contraceptive use before or after infection with *C. trachomatis*. If oral contraceptive use commenced after infection with *C. trachomatis*, then it cannot be said to have increased the risk of infection (except insofar as oral contraceptive use might increase the probability of a test detecting *C. trachomatis*). This inability to identify the temporal relation of oral contraceptive use and chlamydial infection is a form of non-differential

misclassification, which will reduce the power of a case-control study to detect an underlying association.

(3) *Definition of non-exposure.* In many of the studies data are only presented for oral contraceptive use versus all other methods and no contraception grouped together. In some a distinction is made between other methods and no contraception, and in others an analysis is made of several different methods of contraception, including barrier methods. The crude odds ratios shown in table 1 are based on the most common comparison, that is, oral contraceptive use versus non-oral contraceptive use; thus in many cases women using barrier methods are included in the comparison group. If barrier methods are protective, the odds ratios for oral contraceptive use would be spuriously increased. In the meta-analysis we separated out eight studies with information on barrier use, and made a pooled estimate for oral contraceptive versus non-oral contraceptive use excluding barrier methods, and oral contraceptive versus barrier method use.

(4) *Exclusion criteria.* Both antibiotics and pregnancy have an effect on hormone production and metabolism, and antibiotics may eliminate *C. trachomatis*. Thus to include in the study population women who have recently taken antibiotics, or those who are pregnant, might distort the results. Some of the studies, however, excluded only one or the other, or neither.

(5) *Confounding.* Many factors might confound the association between oral contraceptive use and *C. trachomatis*, such as number of sexual partners, age, gravidity, a history of STDs, partner with STD, race, socio-economic status, cervical ectopy. Surprisingly, ten of the studies did not control for confounding in their analysis, possibly because their original aim was not to examine this association. Some study authors collected information on one or more of these factors, and reported that they controlled for them, mostly by univariate analysis. Only four studies reported an adjusted odds ratio for the relationship between *C. trachomatis* and oral contraceptive use.

Thirteen of the studies contained statements to the effect that certain factors were controlled for, but that this made no difference to the findings. For the most part the factors examined were either age or number of partners, or both. We conducted a meta-analysis on these studies as a group also.

There were an additional five studies in which the authors stated that controlling for

Table 3: Pooled estimates of the association between oral contraceptive use and infection with *Chlamydia trachomatis* (29 case control studies published 1974–1990)

	Summary Odds Ratio (95% confidence intervals)	No. of studies
All studies	1.93 (1.77–2.11)	29
High prevalence studies (13% or more)	1.99 (1.71–2.33)	15
Low prevalence studies (less than 13%)	1.90 (1.71–2.11)	14
OC versus barrier methods	2.91 (1.86–4.55)	8
OC versus other methods or none, but excluding barrier	1.64 (1.34–2.00)	9

confounding did make a difference, but did not report any adjusted results. As the adjusted odds ratios were not given in these studies, it was only possible to include the unadjusted ratios in the meta-analysis.

#### Statistical methods

For all studies a crude odds ratio was calculated from the published tables, if not given in the study text, and a 95% confidence interval calculated. In two cases, authors were contacted for the relevant data. The estimate of the summary odds ratio was calculated as a weighted average of the log odds ratio in each study, where the weights for each study were the inverse of the variance calculated from the associated confidence interval. This procedure weights larger studies more heavily than smaller studies in the estimation of the summary odds ratio.<sup>46</sup>

#### Results

A summary listing of the case-control studies is presented in table 1. In 21 studies a statistically significant elevated risk of chlamydial infection was observed among oral contraceptive users as against non-users (those using other methods or none). In a further seven studies a positive association was observed which was not significant.

Three of the case-control studies attempted to deal with the problem of exposure over time. Shafer<sup>12</sup> and Oriel<sup>16</sup> excluded women who had not been taking oral contraceptives for a minimum of six and one month respectively, while Oh<sup>29</sup> measured oral contraceptive use over time, and observed an association of *C. trachomatis* with oral contraceptive use of at least six months (odds ratio = 2.41; 95% confidence interval 1.5–3.29;  $p = 0.005$ ). This association persisted after the authors had controlled for confounding variables including age, gynaecologic age, number of lifetime partners, duration of sex activity and age of current sex partners.

Few studies reported odds ratios adjusted for confounding factors. Apart from the study of Oh mentioned above,<sup>29</sup> Magder<sup>36</sup> controlled for age, race, number of sex partners in the last 30 days, history of sexually transmitted disease, gonorrhoea culture results, and contact with a person who had gonorrhoea, and found a marginally significant increased rate of cervical chlamydial isolation among oral contraceptive users 20 years of age or younger (estimated odds ratio 2.12,  $p = 0.045$ ). Surprisingly, the same model suggested an opposite effect of oral contraceptives in women

older than age 20 years (estimated odds ratio = 0.59,  $p = 0.09$ ). Bro and Juul<sup>40</sup> observed an adjusted odds ratio of 2.02 ( $p = 0.06$ ) among women less than 25 years old.

#### Pooled estimates

In table 3 pooled estimates are presented for the case-control studies. The overall summary crude odds ratio is 1.93 which is highly statistically significant (95% CI 1.77–2.11). The summary odds ratio for studies where it was stated that controlling for confounding did not materially alter the results is also 1.92 (95% CI 1.73–2.12). This is very similar to the summary odds ratio for the studies where no statement about adjusting for confounding was made (1.98 (95% CI 1.67–2.34)). The data for the individual studies are presented graphically, in the figure. An association between the size of the odds ratio and the associated confidence interval is apparent. This reflects the fact that the higher odds ratios are estimated from the smaller studies. The pooling procedure downweights these less precise estimates by combining them with the results from the larger studies which tend to have smaller odds ratios.

When we grouped the studies into those which scored higher on the quality index (median 4 and above), we found no material difference in the pooled estimated odds ratio (OR = 1.89, 95% CI 1.61–2.23), from those studies scoring lower on the quality index (OR = 1.95, 95% CI 1.76–2.16).

It is possible that a low background prevalence may make it easier to detect a small signal than a high background prevalence. Alternatively, we hypothesised that in the lower prevalence groups (from family planning clinics, for instance), many women may not be exposed to *C. trachomatis*, making an associa-

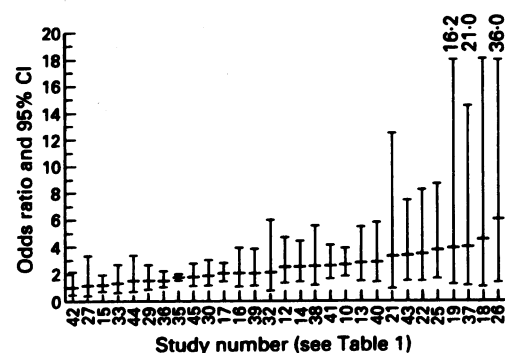


Fig Odds ratios and 95% confidence intervals for 29 case-control studies of the association of oral contraceptive use and infection with *C. trachomatis*

tion with oral contraceptives more difficult to detect. There may be other differences in the studies grouped in this way, such as differences in oral contraceptive prevalence, or age. Dichotomising at the median prevalence of 13%, the pooled estimated odds ratios for studies in the "high prevalence" group (see table 3) was not importantly different from that for studies in the "low prevalence" group. Thus the association we observe does not seem to be a function of prevalence.

Finally, in the pooled analysis if we compare *C. trachomatis* infection in oral contraceptive users with barrier method users, the relative risk is very high—2.91 (1.86–4.55). This suggests that barrier methods are highly protective compared to oral contraceptive use, the inverse odds ratio being 0.34 (95% CI 0.22–0.54). If barrier method users are removed from the comparison group, the observed odds ratio between oral contraceptive use and chlamydial infection is reduced to 1.64 (95% CI 1.34–2.00), a finding which confirms the apparent protective effect of barrier methods. It is possible that barrier users may be different from oral contraceptive users in terms of sex partners, age, or other potentially confounding variables. Unfortunately, confounding is not controlled for in any of these studies. In addition, only one of the eight studies specifies what kinds of barrier methods were used by subjects.<sup>16</sup> Women using barrier methods in Magder's study,<sup>36</sup> were all using the diaphragm. The study could not be included in the pooled estimate, however, because there were no *C. trachomatis* positive women among those using the diaphragm.

#### Prospective studies

The results of the two prospective studies (table 2), are compatible with the meta-analysis findings from the case-control studies. In both studies a positive association between *C. trachomatis* and oral contraceptive use is reported. Louv<sup>24</sup> observed a crude relative risk of 1.95, which dropped to 1.73 when adjusted for number of sex partners. The number of partners was positively correlated ( $p < 0.001$ ) with the probability of chlamydial infection whereas age was negatively correlated ( $p < 0.001$ ). Avonts<sup>31</sup> observed an overall relative risk of 8.8 (with very wide confidence intervals), which, when stratified for number of sex partners, showed an increased risk among oral contraceptive users with more than two partners. Louv<sup>24</sup> found that the crude incidence rate of gonococcal infection was also increased among oral contraceptive users, while in Avonts' study the incidence of gonorrhoea was so low (0.7 episodes/100 women years) that no comparison could be made.

#### The role of cervical ectopy

The principal hypothesised mechanism for oral contraceptives to contribute to chlamydial infection, as mentioned earlier, is that oral contraceptives may produce a greater area of columnar epithelium on the vaginal aspect of the cervix (ectopy), which may be more susceptible to infection with *C. trachomatis*.

Animal studies indicate that both estrogen and progesterone enhance the growth, survival and ascension of genital chlamydial infection, and that progesterone may facilitate infection by preventing loss of target epithelial cells, thus maximising contact with the organism.<sup>11</sup>

In seven of the studies reviewed here the interactions between cervical ectopy, oral contraceptive use and chlamydial infection are examined.<sup>13 15 21 24 30 33 43</sup> The prevalence of ectopy in women in the samples varies from 15.3% to 51.5%.<sup>13 33</sup> In all cases, the presence of ectopy was significantly greater in oral contraceptive users than in non-users, a finding which confirms earlier studies.<sup>47</sup> The positive association between chlamydial infection and cervical ectopy was also statistically significant in those studies reporting on this.<sup>13 15 21 33 43</sup> However, when ectopy, oral contraceptive use and chlamydial infection are examined together, no consistent findings emerge. Four studies<sup>15 21 33 43</sup> report no effect, one<sup>15</sup> reports ectopy and oral contraceptive use seeming to "act additively" on chlamydial isolation, while two<sup>24 30</sup> find that oral contraceptive users without ectopy are still more frequently infected. It therefore remains unclear how important cervical ectopy is in mediating the infection. Harrison's finding<sup>21</sup> that users of barrier contraception had significantly lower prevalence of infection than did users of no contraception, despite very similar degrees of ectopy, confirms the important potential role of barrier methods in protecting against infection.

Cervical ectopy has also been found more frequently in adolescent women.<sup>47</sup> In the studies reviewed, a most consistent finding was that women with chlamydial infection were younger than those with no infection,<sup>10 13 16 21 22 24 25 30–40 43</sup> although the definition of "young" varies. (Four studies found no difference in age of infected versus uninfected women<sup>17 19 28 33</sup> and two found that older age was associated with infection.<sup>33 41</sup>) This suggests that age is a risk factor for chlamydial infection, possibly because of an increased prevalence of cervical ectopy, although confounding by sexual behaviour cannot be ruled out.

In considering this complexity of factors, differences in the ability to detect *C. trachomatis* should be taken into account. Barnes' study<sup>48</sup> comparing individual characteristics with the number of *C. trachomatis* inclusion counts in cervical cultures, found that both youth and oral contraceptive use were associated with higher chlamydial inclusion counts, but no association between cervical ectopy and increased chlamydial counts. This suggests that it may simply be easier to detect chlamydial infection in younger women and oral contraceptive users. The authors conclude that while biologic reasons for these associations between patient attributes and chlamydial inclusion counts remain unknown, the results of studies based on an insensitive measure of disease (such as chlamydial antigen detection systems which are less sensitive than cell culture) must be interpreted cautiously.

## Discussion

In assessing the relationship between the use of oral contraceptives and chlamydial infection, several factors hamper cross-study comparisons. In this analysis we looked for variation in outcome of groups of studies with different characteristics. The pooled estimated unadjusted odds ratio for the 29 studies examined is 1.93 with a lower confidence bound of 1.77, indicating an almost twofold increased risk of chlamydial infection for oral contraceptive users. Neither study quality nor prevalence of *C trachomatis* modified this risk. When compared to the use of barrier contraceptives, however, the risk of infection for women using oral contraceptives increased to 2.91. The pooled estimated protective effect of barrier methods in these studies was 0.34.

The major limitation in a meta-analysis is the quality of the component studies. In this case, few of the studies presented results adjusted for the major potential confounders, age and sexual behaviour. While it was not possible to estimate a pooled odds ratio adjusted for numbers of sexual partners or age, the pooled estimate for thirteen of the studies which contained a statement that controlling for age and number of sex partners made no difference, was similar to the overall pooled estimate and to the estimate for the other studies. The observed pooled relative risk (1.93) is sufficiently large that confounding would have to be substantial to explain the association. In the only prospective study to report data before and after controlling sexual behaviour (Louv<sup>24</sup>), the crude relative risk (1.94) was reduced to 1.73 after adjustment for frequency of coitus, number of partners, age, number of pregnancies, and number of live births. Interestingly, the crude relative risk in this study is very close to the overall pooled estimate for the case-control studies. If the effect of controlling for sexual behaviour in the study of Louv was representative of other studies, then confounding by sexual behaviour only accounts for a small proportion of the excess risk of chlamydial infection associated with oral contraceptive use.

In 52% of the studies young age was associated with increased chlamydial infection, but the question of whether there are more oral contraceptive users who are of young age remains unclear. Cervical ectopy, found more frequently in oral contraceptive users and in those with chlamydial infection, seems to play a mediating role. Different detection techniques may also contribute to biasing estimated relative risks for women with particular characteristics. Additional research is needed to confirm the relationship between ectopy, *C trachomatis* and oral contraceptive use, and to confirm the magnitude of detection bias on relative risk estimates for chlamydial infection.

A further potential problem in meta-analysis is publication bias, a phenomenon in which studies with null, or non statistically significant results may be less likely to be reported and published.<sup>49</sup> The data in the figure suggest that this phenomenon may exist in this analysis; the

smaller studies with wide confidence intervals tend to be "positive" with marginally significant results. There is a lack of small but "null" studies. One explanation is that the larger studies used better methods and more accurately estimated a slightly elevated odds ratios (that is, the high odds ratios in the small studies were confounded). An alternative explanation is that authors are less likely to report null, or non-significant findings. This would result in the pooled findings from the published literature to be a systematic overestimate of the pooled result of all studies actually performed. Publication bias could only be avoided if a complete inventory of all completed studies was available, a requirement which is not fulfilled for this, or any other branch of observational epidemiology.

Any sexually transmitted disease must implicate both sexual partners. It is therefore important to note that while data on numbers of sexual partners which women have was collected in some of these studies, none attempted to assess the sexual behaviour of the women's partners. If the sexual behaviour of partners of women who use oral contraceptives is different in some way, the association of oral contraceptives and *C trachomatis* may potentially be confounded. This one-sided picture of a disease is not only incorrect epidemiologically, but it continues to promote the impression that it is women who are the vectors or transmitters of disease, something which research in the 1990s should be at pains to dispel. Future research in this area needs to take up the challenge to design studies which can investigate the dynamics of chlamydial infection in both sexes.

In the broader context of family planning policies, these findings point strongly to the continued need for promoting barrier methods of contraception. If oral contraceptives do change the cervical epithelium in such a way as to foster chlamydial, and perhaps, other infections in women, the implications for the spread of non-fatal STDs are important, particularly in countries in which STD prevalence is high and oral contraceptives are being promoted to contain population growth. A recent study from Africa<sup>50</sup> reports that *C trachomatis* is a cofactor for HIV transmission. A study in Rwanda<sup>51</sup> and another in Kenya,<sup>52</sup> found HIV infection more frequently among oral contraceptive users. While these findings are far from conclusive, they must at least elicit major public health concern.

Antibodies to *C trachomatis* are associated with increased risk of ectopic pregnancy.<sup>53</sup> Although oral contraceptives have been suggested to protect women infected with *C trachomatis* against acute pelvic inflammatory disease,<sup>54</sup> oral contraceptive users could still be at greater risk of pelvic inflammatory disease (PID) if they are more likely to become infected by *C trachomatis*; the net effect of oral contraceptive use on PID, ectopic pregnancy, and infertility remains to be determined.

Continued research is needed in this complex area to elucidate the precise relationship between chlamydial infection (and other

STDs) and oral contraceptives, and the other factors involved. In particular, more attention must be paid to potential confounding factors. Research is also needed in Africa, Asia and Latin America, where prevalence of both STDs and oral contraceptive use is rising. The results of this meta-analysis, however, do support the conclusion that oral contraceptive use is associated with increased risk of chlamydial infection even after adjusting for the protective effect of barrier methods. This finding emphasises the importance of considering the risks and benefits of oral contraceptive use among women who are likely to be exposed to *C. trachomatis* and other STDs. The strong protective effect of barrier methods confirmed in this meta-analysis highlights the importance these methods have for reducing both individual risk, and the community burden of STDs.

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